PROCESS FOR THE OXIDATION OF UNSATURATED ALCOHOLS

Cross-Reference to Related Applications

This application is a continuation of International Application PCT/IB03/00139 filed January 15, 2003, the entire content of which is expressly incorporated herein by reference thereto.

Technical field

The present invention relates to the field of organic synthesis and more precisely to a process for the synthesis of an unsaturated aldehyde or ketone by oxidation of the corresponding alcohol. The oxidation is performed by a hypochlorite salt and a catalytic amount of an N-(2,2,6,6-tetraalkyl-4-piperidinyl-N-oxyl)-2-amino-1,3,5-triazine derivative, preferably an N-oxyl derivative of one of the polymers known under the trademark Chimassorb® 944 or 2020 (origin: Ciba Specialty Chemicals, Basel, Switzerland).

Background Art

The oxidation of an alcohol into the corresponding aldehyde or ketone by a hypochlorite salt and in the presence of an N-oxyl derivative as catalyst is a very attractive process for the chemical industry as it involves inexpensive and readily available oxidants and catalysts.

However, the prior art in this field proves that only saturated, benzylic or arylalkyl alcohols can be oxidized with good yield using such a process. Indeed, the use of unsaturated alcohols, e.g., those having an alkenyl group, is quite rare and results always in very low yields, if any. Thus, there is a need for improved processes of these types.

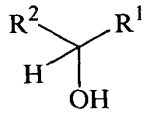
Summary of the Invention

In order to overcome the problems aforementioned, the present invention relates to a catalytic process, with high yields, for the oxidation of unsaturated alcohols allowing the use of a hypochlorite compound as a secondary oxidant.

The process of the invention concerns more specifically the oxidation of an unsaturated alcohol into the corresponding unsaturated aldehyde or ketone in the presence of an effective amount of a hypochlorite salt and a N-(2,2,6,6-tetraalkyl-4-piperidinyl-N-

oxyl)-2-amino-1,3,5-triazine derivative as catalyst. By "unsaturated alcohol" it is meant an alcohol having one or more non-aromatic carbon-carbon double bond.

More precisely, the process of the invention concerns the oxidation of an unsaturated alcohol, or substrate, of formula



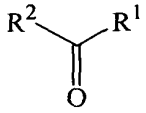
(I)

R^1 represents a hydrogen atom, a C_1 to C_{20} linear, branched or cyclic saturated or unsaturated hydrocarbon group, said hydrocarbon group optionally being substituted and also optionally including one or two oxygen or nitrogen atoms;

R^2 represents a C_2 to C_{20} linear, branched or cyclic alkenyl, alkandienyl or alkantrienyl hydrocarbon group, said hydrocarbon group optionally being substituted and also optionally including one or two oxygen or nitrogen atoms; or said R^1 and R^2 optionally may be bonded together to form an unsaturated ring having 5 to 20 carbon atoms, said ring optionally being substituted and also optionally including one or two oxygen or nitrogen atoms;

wherein the optional substituents of R^1, R^2 and of the ring which said R^1 and R^2 together may optionally form, are C_1 to C_{15} linear, branched or cyclic alkyl, alkenyl or aromatic groups;

into a corresponding unsaturated aldehyde or ketone of formula



(II)

wherein R^1 and R^2 are as defined in formula (I);

wherein the oxidation is performed by a hypochlorite salt of formula

$$M(OCl)_n \qquad \text{(III)}$$

in which M represents an alkaline metal, in which case n is 1, or an alkaline-earth metal in which case n is 2;

and in the presence of a catalytic amount of a N-(2,2,6,6-tetraalkyl-4-piperidinyl-N-oxyl)-2-amino-1,3,5-triazine compound.

As optional ingredients, one of a bromide salt of formula M'Br or a bicarbonate of formula $M'HCO_3$ may be added to the process of the invention, wherein M' is an alkaline metal.

Detailed Description of the Preferred Embodiments

A preferred unsaturated alcohol, and the correspondingly preferred unsaturated aldehyde or ketone, is a compound of formula (I), or (II) respectively, wherein R^1 represents a hydrogen atom, a C_1 to C_{15} linear, branched or cyclic saturated or unsaturated hydrocarbon group possibly substituted and also possibly comprising one or two oxygen atoms;

R^2 represents a C_2 to C_{15} linear, branched or cyclic alkenyl, alkandienyl or alkantrienyl hydrocarbon group, possibly substituted and possibly comprising one or two oxygen atoms; or said R^1 and R^2 may be bonded together to form an unsaturated ring having 5 to 20 carbon atoms, said ring being possibly substituted and possibly comprising one or two oxygen or nitrogen atoms; and

the possible substituents of R^1, R^2 and of the ring which said R^1 and R^2 may form together, are C_1 to C_{10} linear, branched or cyclic alkyl, alkenyl or aromatic groups;

In a particularly attractive embodiment of the invention, the unsaturated alcohol, and the corresponding unsaturated aldehyde, is a compound of formula (I), or (II) respectively, wherein R^1 represents a hydrogen atom;

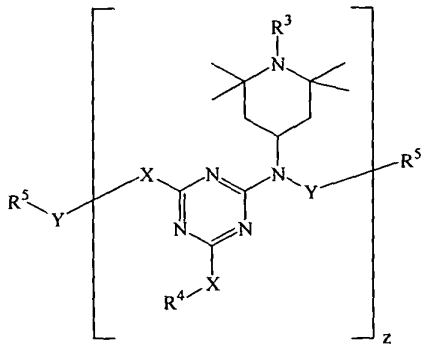
R^2 represents a C_5 to C_{15} linear, branched or cyclic alkenyl or alkandienyl hydrocarbon group, possibly substituted; or R^2 represents a C_7 to C_{15} linear, branched or cyclic alkantrienyl hydrocarbon group possibly substituted; and

the possible substituents of R^2 are C_1 to C_8 linear, branched or cyclic alkyl, alkenyl or aromatic groups.

The hypochlorite salt is preferably selected from the group consisting of NaOCl, KOCl and $Ca(OCl)_2$.

The bromide salt is preferably KBr or NaBr. Preferred bicarbonates are $KHCO_3$ or $NaHCO_3$.

The N-(2,2,6,6-tetraalkyl-4-piperidinyl-N-oxyl)-2-amino-1,3,5-triazine compound, the catalyst, is preferably a compound of formula



(IV)

wherein z represents an integer from 1 to 20;

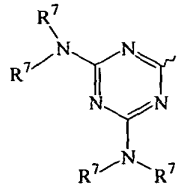
R^3 represents, simultaneously or independently, a hydrogen atom or an oxyl radical (O), with the proviso that at least one R^3 group is an oxyl radical;

X represents an oxygen atom or a $-NR^4-$ group;

R^4 represents, simultaneously or independently, a hydrogen atom, a 2,2,6,6-tetramethyl-4-piperidinyl group, a 2,2,6,6-tetramethyl-4-piperidinyl-N-oxyl radical group or a C_1 to C_{15} linear, branched or cyclic saturated or unsaturated hydrocarbon group, said hydrocarbon group being possibly comprising one or two oxygen or nitrogen atoms; or two R^4 groups, bonded to the same nitrogen atom, may be bonded together to form a heterocycle having 5 to 7 members and which may contain an oxygen atom;

R^5 represents, simultaneously or independently, a hydrogen atom or a NR^6_2 group;

R^6 represents, simultaneously or independently, a hydrogen atom, a C_1 to C_{20} linear, branched or cyclic saturated or unsaturated hydrocarbon group, a 2,2,6,6-tetramethyl-4-piperidinyl-N-oxyl radical group, a 2,2,6,6-tetramethyl-4-piperidinyl group or a group of formula

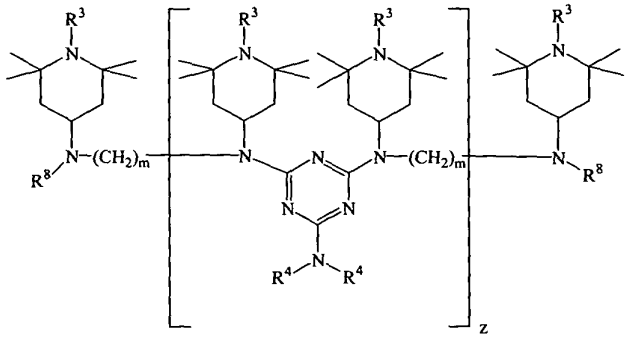


(V)

R^7 representing, simultaneously or independently, a hydrogen atom, a C_1 to C_{12} linear or branched alkyl group, a 2,2,6,6-tetramethyl-4-piperidinyl-N-oxyl radical group or a 2,2,6,6-tetramethyl-4-piperidinyl group; and

Y represents, simultaneously or independently, a C_2 to C_{20} linear, branched or cyclic alkylene group possibly comprising one or two oxygen or nitrogen atoms.

More preferably, the catalyst is a polymeric or oligomeric compound of formula



(IV')

wherein z represents an integer from 2 to 10;

m represent an integer from 2 to 12;

R^3 is as defined in formula (IV);

R^4 represents, simultaneously or independently, a hydrogen atom, a 2,2,6,6-tetramethyl-4-piperidinyl-N-oxyl radical group, a 2,2,6,6-tetramethyl-4-piperidinyl group or a C_1 to C_{10} linear or branched alkyl or alkenyl group; or two R^4 groups, bonded to the same nitrogen atom, may be bonded together to form a heterocycle having 6 members and which may contain an oxygen atom; and

R^8 represents, simultaneously or independently, a hydrogen atom, a C_1 to C_{10} linear or branched alkyl or alkenyl group, a 2,2,6,6-tetramethyl-4-piperidinyl-N-oxyl radical group, a 2,2,6,6-tetramethyl-4-piperidinyl group or a group of formula (V) as defined previously.

Even more preferably, the catalyst is a N-oxyl derivative of the polymers having the CAS Registry Numbers 71878-19-8 or 192268-64-7 and which are also known under the trademark Chimassorb® 944 or 2020 respectively (origin: Ciba Specialty Chemicals, Basel, Switzerland). One of said derivatives of the Chimassorb® 944 is known in the literature with the name PIPO and has the CAS Registry Number 91993-31-6.

In a general way, the catalyst of formula (IV) can be prepared and isolated prior to its use according to the general methods described in the literature (E.G. Rozantsev *et al.* in Synthesis **1971**, 190, or in the patent application FR 2788272).

Moreover, the catalyst of formula (IV) can be prepared *in situ*, i.e. in the reaction medium, by using the same methods mentioned herein above without isolation or purification, just before their use.

The catalyst of formula (IV) can be added to the reaction medium in a large range of concentrations. As non-limiting examples, one can cite as catalyst concentration

values ranging from 0.02 to 0.15 molar equivalents, relative to the amount of alcohol of formula (I), preferably between 0.03 and 0.1 molar equivalents. It goes without saying that the optimum concentration of catalyst will depend on the nature of the latter and on the alcohol of formula (I) used during the process, and that a person skilled in the art will be able to define said optimum concentration by carrying out routine experiments.

Concerning the quantities of the hypochlorite salt, which can be added to the reaction mixture, one can cite, as non-limiting examples, ranges between 0.9 and 2.5 molar equivalents, relative to the amount of alcohol of formula (I), preferably between 0.9 and 1.5 molar equivalents. In the case the substrate is a primary alcohol, then particularly useful concentrations of hypochlorite salt may range preferably between 1.0 and 1.3 molar equivalents. Again the optimum concentration of hypochlorite salt will depend on the nature of the latter and on the alcohol of formula (I) used during the process, therefore a person skilled in the art will be able to define said optimum concentration by carrying out routine experiments.

The bromide salt M'Br may be added in a quantity ranging between 0 and 0.05 molar equivalents relative to the amount of alcohol of formula (I), preferably between 0.005 and 0.015 molar equivalents.

The bicarbonate $M'HCO_3$ may be added in a quantity ranging between 0 and 0.2 molar equivalents relative to the amount of alcohol of formula (I), preferably between 0.05 and 0.15 molar equivalents.

The oxidation reaction can be carried out in the presence or absence of a solvent. When a solvent is required or used for practical reasons, then any solvent currently used in reactions where an alcohol is oxidized can be employed for the purposes of the invention, provided that the starting alcohol of formula (I) and the N-(2,2,6,6-tetraalkyl-4-piperidinyl-N-oxyl)-2-amino-1,3,5-triazine derivative are at least partially soluble. Non-limiting examples include aromatic solvents such as benzene, toluene or xylene, hydrocarbon solvents such as hexane or cyclohexane, dialkyl ethers such as methyl terbutyl ether, C_1 to C_6 alkyl acetate such an ethyl or propyl acetate, chlorinated solvents such as dichloromethane or chloroform, or mixtures thereof. A person skilled in the art is well able to select the most convenient solvent in each case to optimize the oxidation reaction, however ethyl or propyl acetate, dichloromethane or toluene is the preferred solvents.

The temperature at which the process of the invention can be carried out may be comprised in a large range of concentrations. As non-limiting examples, one can cite

temperature ranging between 0 °C and 60°C, preferably in the range between 15°C and 40°C. Of course, a person skilled in the art is also able to select the optimum temperature, taking into account, e.g., the melting and boiling point of the catalyst, starting and final products as well as of the solvent.

It is noteworthy that the process according to the invention, in addition to its characteristic high yields, presents also the advantage of producing low quantities of chlorinated by-products, which are frequently undesired impurities, to the contrary of the prior art processes using hypochlorite salts. In general terms, such chlorinated by-products represent less than 5% of yield, and frequently even less than 3%.

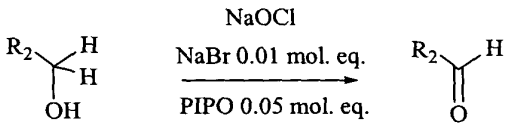
Examples

The invention will now be described in further detail by way of the following examples, wherein the abbreviations have the usual meaning in the art, the temperatures are indicated in degrees centigrade (°C).

Example 1: Oxidation of primary alcohols containing double bonds with NaOCl catalyzed by PIPO (N-oxyl derivative of Chimassorb® 944)

PIPO can be obtained according to any of the methods reported in the literature, e.g. the patent application FR 2788272 or Dijksman *et al.* in Synlett **2001**, 102-4.

General procedure:



In a 100 ml round bottomed flask were charged PIPO (0.05 molar equivalents) and NaBr (20% aqueous solution; 0.01 molar equivalents) followed by the alcohol to be oxidized (10 g, 1 molar equivalents) and ethyl acetate as solvent (35 g). After dissolution of PIPO, it was introduced over one hour, at room temperature, an aqueous solution containing NaOCl (1.1-1.45 molar equivalents) and in which $NaHCO_3$ (2% weight/weight relative to NaOCl solution) was added just before use. At the end of the introduction, the stirring was continued for 15-45 min and afterwards the reaction mixture was allowed to stand until the phase separation. The aqueous phase was removed, and the organic phase was washed with water. Then, the organic phase was concentrated under vacuum and the

clear orange crude product was purified by distillation (bulb-to-bulb) to afford the corresponding aldehyde. The aldehydes obtained had all the same spectroscopic data as reported in the literature.

The results obtained for the oxidation of some unsaturated alcohols are summarized below in Table 1.

Table 1 : Results of the oxidation of some unsaturated alcohols into the corresponding aldehydes using NaOCl and PIPO as catalyst

Alcohol [a)]	**Aldehyde** [a)]	**Conversion of the alcohol (%)**	**Yield of the aldehyde (%)**	**NaOCl** [b)]
1a	1b	99.5	90	1.05
1a [i)]	1b	79	20	1.25
2a	2b	100	99	1.05
3a	3b	97	70	1.45
4a [ii)]	4b	99	77	1.25
5a	5b	89	81	1.10
5a [iii)]	5b	86	81	1.10
5a [iv)]	5b	55	-	1.10
6a	6b	98	82	1.18
7a	7b	90	77	1.30
7a [v)]	7b	5	-	1.30

a) alcohol or aldehyde of formula (II) or (I) respectively:

1a : 3-Phenyl-2-propen-1-ol	1b : 3-Phenyl-2-propenal
2a : (E)-2-Dodecen-1-ol	2b : (E)-2-Dodecenal
3a : 3,7-Dimethyl-2,6-octadien-1-ol	3b : 3,7-Dimethyl-2,6-octadienal
4a : (2E,4Z,7Z)-2,4,7-Decatrien-1-ol	4b : (2E,4Z,7Z)-2,4,7-Decatrienal
5a : (Z)-5-Octen-1-ol	5b : (Z)-5-Octenal
6a : 10-Undecen-1-ol	6b : 10-Undecenal

7a : 3-(4-Tert-butyl-1-cyclohexen-1-yl)-1-propanol 7b : 3-(4-Tert-butyl-1-cyclohexen-1-yl)-propanal

b) molar equivalent, relative to the amount of alcohol

i) in CH2Cl2, in the presence of 0.1 molar equivalent of KBr and with 0.01 molar equivalent of 4-methoxy-2,2,6,6-tetraalkyl-piperidine-N-oxyl (P. L. Anelli, C. Biffi, F. Montanari and S. Quici, *J. Org. Chem.* **1987**, *52*, 2559).

ii) in CH_2Cl_2, with 0.1 molar equivalent of PIPO.

iii) in the absence of NaBr.

iv) with 0.03 molar equivalent of 2,2,6,6-tetraalkyl-piperidine-N-oxyl.

v) with 0.01-0.1 molar equivalent of 2,2,6,6-tetraalkyl-piperidine-N-oxyl.

Example 2: Oxidation of an unsaturated secondary alcohol with NaOCl catalyzed by PIPO (N-oxyl derivative of Chimassorb® 944)

In a 100 ml round bottomed flask were charged PIPO (0.029 molar equivalents) and NaBr (20% aqueous solution; 0.01 molar equivalents) followed by isophorol (5 g, 1 molar equivalents) and ethyl acetate as solvent (13 g). After dissolution of PIPO, it was introduced over approximately one hour, at room temperature, an aqueous solution containing NaOCl (2.0 molar equivalents) and in which $NaHCO_3$ (0.7 g) was added just before use. At the end of the introduction, the stirring was continued for 30 min and afterwards the reaction mixture was allowed to stand until the phase separation. The aqueous phase was removed, and the organic phase was washed with a 5% water solution of ascorbic acid. Then, the organic phase was concentrated under vacuum and the clear yellow crude product was purified by distillation (bulb-to-bulb) to afford the corresponding aldehyde. It was thus obtained isophorone in 62% yield (conversion of the starting material = 87%).